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ORIGINAL ARTICLE

Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides

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Abstract

Introduction Mycosis fungoides (MF) is a non-Hodgkin's T-cell lymphoma of the skin that often begins as limited patches and plaques with slow progression to systemic involvement. Narrowband ultraviolet (UV) B therapy has been proven to be an effective short-term treatment modality for clearing patch-stage MF. The effect of psoralen plus long-wave ultraviolet A (PUVA) in the treatment of patch- and plaque-type MF has also been thoroughly documented.

Objectives The purpose of this study was to compare the efficacy and safety of narrowband UVB and PUVA in patients with early-stage MF.

Methods We analysed the response to treatment, relapse-free survival and irradiation dose in 114 patients with histologically confirmed early-stage MF (stage IA, IB and IIA).

Results A total of 95 patients were treated with PUVA (83.3%) and 19 with narrowband UVB (16.7%). With PUVA, 59 patients (62.1%) had a complete response (CR), 24 (25.3%) had a partial response (PR) and 12 (12.6%) had a failed response. Narrowband UVB led to CR in 12 (68.4%) patients, PR in 5 (26.3%) patients and a failed response in 1 (5.3%) patient. There were no differences in terms of time to relapse between patients treated with PUVA and those treated with narrowband UVB (11.5 vs. 14.0 months respectively; $P = 0.816$). No major adverse reactions were attributed to the treatment.

Conclusions Our results confirm that phototherapy is a safe, effective and well-tolerated, first-line therapy in patients with early-stage cutaneous T-cell lymphoma, with prolonged disease-free remissions being achieved. It suggests that narrowband UVB is at least as effective as PUVA for treatment of early-stage MF.

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Keywords

disease-free survival, mycosis fungoides, narrowband UVB therapy, phototherapy, PUVA therapy

Conflict of interest

None declared.

Introduction

Cutaneous T-cell lymphoma (CTCL) describes a heterogeneous group of neoplasms of skin-homing T cells that show considerable variation in clinical presentation, histological appearance, immunophenotype and prognosis. Mycosis fungoides (MF) is the most common form of CTCL and accounts for approximately 50% of all primary cutaneous lymphomas, with an estimated incidence of 0.3/100 000 inhabitants per year.[1]

Early-stage MF presents as erythematous, slightly scaling patches or plaques, in a limited or generalized distribution, with no systemic involvement. It has been treated with various agents, including topical potent corticosteroids, topical nitrogen mustard, topical carmustine, electron-beam radiotherapy, interferon-α, retinoids and topical bexarotene.[2] Based on the frequent occurrence of lesions in non-exposed areas, ultraviolet (UV) radiation therapy has long been used to induce remission in those patients. Broadband UVB and psoralen plus ultraviolet A (PUVA) have been widely used modalities for treatment of MF, but psoralen-related side-effects and long-term risk of photocarcinogenesis are not negligible.[3] As successful use of narrowband UVB phototherapy for MF is being reported,[4–11] this treatment option has become more widespread. In psoriatic patients, as they represent the largest group of patients receiving phototherapy, narrowband UVB is reported to have the same efficacy when compared with PUVA, but with fewer side-effects,[12] and reduced risk of carcinogenicity.[13]

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We therefore decided to conduct a retrospective study of our experience to determine how the use of narrowband UVB compares with that of PUVA for early-stage MF.

Materials and methods

Patient population

A retrospective search of the patient database of the Photodermatology Unit in the Department of Dermatology of Hospital dos Capuchos was carried out to identify patients with histologically proven early-stage MF who were treated for the first time with either PUVA or narrowband UVB. All patients had stage IA, IB or IIA disease. The stage of the disease was determined on the basis of the type and extent of skin involvement, according to the European Organization of Research and Treatment of Cancer (EORTC).[14] Stage IA refers to MF confined to the skin with patches and plaques covering less than 10% of the skin surface (T1N0M0 in the TNM classification). Stage IB refers to MF confined to the skin with equal to or more than 10% of patches and plaques covering the skin surface (T2N0M0). Stage IIA refers to MF in the skin with equal to or more than 10% of patches and plaques covering the skin surface, and clinically abnormal peripheral lymph nodes but negative pathology for CTCL (T1-2N1M0).

All patients were evaluated by an ophthalmologist prior to the start of phototherapy. Selection was not made according to severity of disease. Patients with significant comorbidities or contraindications to psoralen use were preferably treated with narrowband UVB.

Database records and patient medical charts were reviewed to obtain data on gender, age, skin phototype, pre-treatment disease stage, pre-treatment disease duration (considered clinically), PUVA treatment regimen (psoralen dose, cumulative UVA dose, treatment duration and number of treatments), narrowband UVB treatment regimen (cumulative UVB dose, treatment duration and number of treatments), treatment response and side-effects.

Treatment

Psoralen plus long-wave ultraviolet A therapy was conducted twice a week, at least 3 days apart. The UVA radiation was administered 2 h after the intake of 8-methoxypsoralen 0.6 mg/kg. The initial doses of UVA were chosen according to Fitzpatrick's skin type: 1 J/cm^2 for skin type II, 1.5 J/cm^2 for skin type III and 2 J/cm^2 for skin type IV. Successive exposures were adjusted to skin reactions and skin type. In patients with skin types III and IV, if the previous exposure had not caused a noticeable effect, the next exposure time was increased by 30%; if the previous exposure induced a doubtful erythema, it was increased by 10% and if it caused a slight erythema, the same exposure time was repeated. In patients with skin types I and II, the dose increments were 15% and 5% for no erythema and slight erythema respectively. Maximum UVA dose per treatment was not higher than 10 J/cm^2. Therapy was continued until more than 95% clearing of the patient's skin lesions had occurred (clearing phase). Maintenance phase started once the response had reached a plateau: treatment was continued for another 8 weeks, and then reduced to weekly sessions for another 4–8 weeks. If the patient remained more than 95% clear, treatment was then discontinued. For patients who achieved less than 95% clearance, PUVA treatment was continued until no further clinical improvement was noted.

Narrowband UVB therapy was conducted thrice a week on non-consecutive days. The first exposure given was 70% of the predetermined minimal erythema dose on the trunk. Dose escalation at each visit was made according to the previous erythema response. If there was no erythema, 20% increments were made. For barely perceptible erythema, the previous dose was repeated. For well-defined erythema, one session was postponed, the same dose was repeated and increments were reduced to 10%. In the presence of painful erythema or bulla, sessions were postponed until recovery; thereafter a decrease of 50% in the dose was made and the regimen was changed to minimal increments in the following sessions. As with PUVA, narrowband UVB was continued until more than 95% clearing was achieved. Maintenance therapy was then started by tapering the frequency of the sessions: twice a week for 4–8 weeks, and then weekly for another 4–8 weeks. Treatment was discontinued if the patient remained clear. For patients who responded incompletely (less than 95% clearance), therapy was maintained until no additional clinical benefit was reported.

Association of systemic therapies (retinoids, corticosteroids or methotrexate) was not accounted as an exclusion criterion, but was considered when evaluating treatment response. These cases fell into two possible situations: patients were either unresponsive to systemic therapies and phototherapy was then started, or patients were unresponsive to phototherapy and a systemic therapy was then initiated.

Evaluation of response and toxicity

Response was evaluated according to clinical criteria. Complete response (CR) was defined as more than 95% clearing of skin lesions; partial response (PR) was considered when more than 50% clearing of lesions was achieved, despite continuing treatment; no response was described as less than 50% clearing of skin lesions, with persistent skin disease despite continuing treatment. Relapse was defined as clinically significant disease requiring further therapy. Side-effects, and local and systemic toxicity were recorded during the therapy.

Statistical analysis

Baseline characteristics, clinical response and recurrence rates of patients treated with PUVA vs. narrowband UVB were compared using the chi-squared test, Fisher's exact test or independent samples *t*-test, as appropriate. Kaplan–Meier lifetime table analysis was performed to plot relapse-free rates after phototherapy modalities, and the log-rank test was used to compare them between

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treatment groups. Relapse-free survival (RFS) was defined as time from treatment completion to local and/or systemic progression. *P*-values <0.05 were considered to be significant. All analyses were performed using the SPSS 12.0 for Windows (2003, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 114 patients with early-stage MF were treated with either PUVA or narrowband UVB at our department between September 1996 and January 2007. Of these patients, 95 (46 men and 49 women; mean age 59 years, range 30–80 years) were treated with PUVA and 19 (6 men and 13 women; mean age 68 years, range 31–87 years) were treated with narrowband UVB. The disease stage of the patients was as follows: PUVA group, IA ($n = 31$), IB ($n = 57$) and IIA ($n = 7$), and narrowband UVB group, IA ($n = 6$), IB ($n = 12$) and IIA ($n = 1$). The mean disease duration before treatment was 56.4 months in the PUVA group vs. 65.8 months in the narrowband UVB group. Except for the age, no single baseline characteristic was significantly different between the two groups, which accounts for the homogeneity between them. Patients' clinical data are summarized in Table 1.

Treatment outcome

No statistically significant differences in response were found between the two phototherapy regimens: PUVA treatment led to CR in 59 of 95 (62.1%) and PR in 24 of 95 (25.3%) patients, whereas narrowband UVB treatment led to CR in 13 of 19 (68.4%) and PR in five of 19 (26.3%) patients (Table 2); there were 12 non-responders or patients with disease progression in the PUVA group (12.6%), and one in the narrowband UVB group (5.3%) ($P = 0.650$).

There were no significant differences between the two groups in terms of treatment duration (PUVA 15.6 months vs. narrowband UVB 12.3 months, $P = 0.248$), number of treatments (PUVA 31 treatments vs. narrowband UVB 37 treatments, $P = 0.382$) or associated therapies (monotherapy: 39 vs. 12 patients, retinoids: 51 vs. 7 patients, corticosteroids: 3 vs. 0 patients, methotrexate: 2 vs. 0 patients; PUVA group vs. narrowband group respectively). In the narrowband UVB group, neither treatment duration (14.9 vs. 7.7 weeks; $P = 0.183$), nor the cumulative UVB dose (80.9 vs. 60.6 J/cm^2; $P = 0.163$) was significantly shortened by the association with systemic therapies; however, in the PUVA group, the use of systemic therapies was associated with longer treatment durations (12.2 vs. 18.1 weeks; $P = 0.014$) and higher cumulative UVA doses (144.7 vs. 93.7 J/cm^2; $P = 0.001$). The total narrowband UVB irradiation dose ranged from 24 to 135 J/cm^2 (mean: 73.4 J/cm^2) and the total UVA dose ranged from 30 to 455 J/cm^2 (mean: 123.8 J/cm^2).

Disease recurrence was observed in 75 of 83 (90.4%) PUVA-treated responder patients and 15 of 18 (83.3%) narrowband UVB-treated responder patients ($P = 0.307$). Two of the PUVA-treated responder patients had systemic progression of the disease: it occurred 4 months after discontinuing therapy by detection of clinically and pathologically abnormal peripheral lymph nodes. There were two other patients also in the PUVA group with systemic progression, but they were non-responders. The mean relapse-free interval for responder patients treated with PUVA ($n = 83$) was 11.5 ± 1.5 months (relapse-free rate at 1 year: 30.5%) and for patients treated with narrowband UVB ($n = 18$), 14.0 ± 4.9 months (relapse-free rate at 1 year: 43.8%). Kaplan–Meier lifetime table analysis revealed no significant difference in

Table 1 Clinical characteristics of study patients with early-stage mycosis fungoides

		PUVA ($n = 95$)	Narrowband UVB ($n = 19$)
Gender, *n* (%)	Male	46 (48.4)	6 (31.6)
	Female	49 (51.6)	13 (68.4)
Phototype, *n* (%)	II	27 (28.4)	7 (36.8)
	III	64 (67.4)	10 (52.6)
	IV	3 (3.2)	2 (10.5)
	V	1 (1.1)	0
Stage, *n* (%)	IA	31 (32.6)	6 (31.6)
	IB	57 (60.0)	12 (63.2)
	IIA	7 (7.4)	1 (5.3)
Mean age*, years (range)		58.8 (30.6–80.0)	68.0 (31.0–87.7)
Mean weight, kg		69.6 ± 10.9	68.8 ± 15.2
Mean disease duration, months (range)		56.4 (3–196)	65.8 (20–168)

PUVA, psoralen plus ultraviolet A; UVB, ultraviolet B.
*$P < 0.005$.

Table 2 Overall results of photo(chemo)therapy in mycosis fungoides

	PUVA ($n = 95$)	Narrowband UVB ($n = 19$)
Clinical response		
CR	59 (62.1)	13 (68.4)
PR	24 (25.3)	5 (26.3)
Mean treatment duration (months)	15.6	12.3
Mean number of treatments	31	37
Mean irradiation dose (J/cm^2)	123.8	73.4
Associated therapies		
None	39 (41.1)	12 (63.2)
Retinoids	51 (53.7)	7 (36.8)
Corticosteroids	3 (3.2)	0
Methotrexate	2 (2.1)	0
Mean relapse-free interval (months)	11.5	14.0

Values in parentheses are percentages.
PUVA, psoralen plus ultraviolet A; UVB, ultraviolet B; CR, complete response; PR, partial response.

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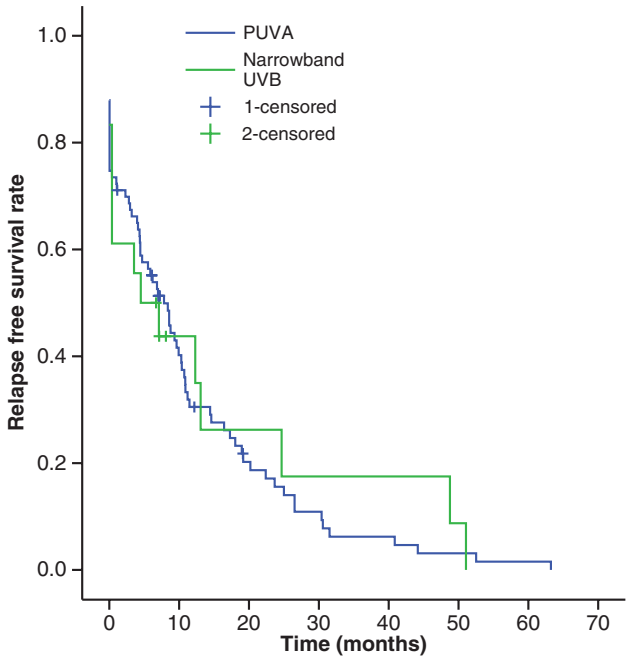

Figure 1 Kaplan–Meier analysis of relapse-free interval of responder patients with mycosis fungoides after psoralen plus ultraviolet A therapy (n = 83) or narrowband ultraviolet B (n = 18). There was no significant difference in the time to relapse between the two groups (P = 0.816; log-rank test).

the time to relapse between the two groups (P = 0.816) (Fig. 1). Disease stage and the association of systemic therapies did not influence relapse-free interval after treatment (P = 0.712 and 0.361 respectively), regardless of the type of phototherapy used. The main treatment outcomes for treatment groups according to stage of the disease are presented in Table 3; no statistically significant differences were found between all the parameters tested.

Safety

A total of 18 patients treated with PUVA (18.9%) reported burning sensation or generalized erythema that impeded subsequent treatment, four of them with blisters. Treatment had to be stopped in two of these patients (2.1%) because of adverse events: one with blisters on the hands, the other with generalized burning without blistering. Gastrointestinal complaints occurred in three patients after systemic psoralen intake. Three patients reported severe pruritus and one had an easily controlled polymorphic light eruption.

Acute adverse effects reported from narrowband UVB were burning in two patients (10.5%). One of them (5.3%) had to discontinue treatment. No statistically significant differences in adverse events were found between the groups (P = 0.784).

Discussion

Narrowband UVB is being integrated into the therapeutic approaches of early-stage CTCL.[15] The success that is being reported by several authors prompted us to evaluate the effectiveness and safety of this treatment compared with that of the well-established PUVA therapy.

This study shows that both narrowband UVB and PUVA achieve similar results in terms of CR rates (68% vs. 62%). There were no significant differences in duration (12.3 vs. 15.6 months) and number of treatments (37 vs. 31), in the relapse rate (83% vs. 90%) or in the mean time to relapse after a response (14 vs. 11.5 months). Our narrowband UVB results are in accordance with other published reports (Table 4). These overall results are somewhat negatively biased by the inclusion of patients in stage IIA who, in theory, would respond poorly to phototherapy. Actually, these patients (seven in PUVA group and one in narrowband UVB group) had lower CR rates and shorter RFS, but their relative weight in the analysis does not change the global tendency.

In a retrospective study comparing narrowband UVB and PUVA treatment of early-stage (stages IA and IB) MF, Diederen *et al.*[16] also found no differences between CR rates [81% (17 of 21 patients) vs. 71% (25 of 35 patients)], or mean relapse-free interval (24.5 vs. 22.8 months). In another study, Ahmad *et al.*[17] treated 12 patients with MF (stage IA–IIB) with narrowband UVB and 28 patients with PUVA. Similar conclusions were drawn: six patients (50%) had a CR to narrowband UVB and 18 (64%) had a CR to PUVA; the median relapse-free interval was 11.5 months in the first group and 10 months in the second. In a prospective

Table 3 Results of photo(chemo)therapy in mycosis fungoides according to stage

	PUVA (n = 95)					Narrowband UVB (n = 19)				
	n	Treatment duration (weeks)	Total dose (J/cm^2)	Clinical response	Relapse-free interval (months)	n	Treatment duration (weeks)	Total dose (J/cm^2)	Clinical response	Relapse-free interval (months)
IA	31	16.9	127.6	CR 20 (64.5) PR 8 (25.8)	10.6	6	11.5	84.8	CR 5 (83.3) PR 1 (16.7)	18.9
IB	57	14.1	119.6	CR 37 (64.9) PR 15 (26.3)	12.1	12	12.6	69.2	CR 8 (66.7) PR 3 (25.0)	13.2
IIA	7	22.7	141.1	CR 2 (28.6) PR 1 (14.4)	7.6	1	12.4	55.1	CR 0 PR 1 (100)	1.0

Values in parentheses are percentages.

PUVA, psoralen plus ultraviolet A; UVB, ultraviolet B; CR, complete response; PR, partial response.

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Table 4 Results of narrowband UVB treatment in early-stage mycosis fungoides compared with literature data

Narrowband UVB	No. patients	CR rate (%)	PR rate (%)	RFS (months)
Hofer *et al.*[4]	20	95	5	6
Clark *et al.*[5]	8	75	25	20
Gathers *et al.*[6]	24	54	29	13
Ghodsi *et al.*[7]	16	75	19	5
Pavlotsky *et al.*[8]	68	81	6	NA
Brazelli *et al.*[9]	20	90	10	8
Boztepe *et al.*[10]	14	78	7	26
Gökdemir *et al.*[11]	23	91	9	11
This study	19	68	26	14

RFS, relapse-free survival; NA, not available; UVB, ultraviolet B; CR, complete response; PR, partial response.

right–left comparative study, El-Mofty *et al.*[18] tried to determine whether the addition of psoralen into a narrowband UVB regimen was superior to narrowband UVB alone in treating early-stage MF, when compared with PUVA. They chose 20 patients and divided them into two equal groups: group I received narrowband UVB on the right body half vs. PUVA on the left side of the body, and group II received psoralen with narrowband UVB on the right side of the body vs. PUVA on the left side. They confirmed that both narrowband UVB regimens were as effective as PUVA, but that the association of psoralen with UVB did not enhance its therapeutic efficacy.

One of the variables these three previous comparative studies did not clearly address was the concomitant use of systemic therapies. In our study, seven of the 19 patients (37%) of the narrowband UVB group had combination regimens, against 56 of 95 patients (59%) of the PUVA group. One of the aims of combination therapy is to lower the cumulative dose and number of treatments, enhancing efficacy with higher remission rates and relapse-free intervals.[15,19] However, treatment duration and cumulative doses were not significantly affected in the narrowband UVB group. Paradoxically, we registered longer treatment durations and cumulative radiation doses in the PUVA group. This finding is probably a consequence of systemics being preferentially used whenever a patient had a more severe or less responsive MF. However, no differences in relapse-free intervals between patients on phototherapy associated with a systemic agent and phototherapy alone were found in our study, which is in line with previous reports.[15,19]

The mechanisms by which PUVA induces tumour regression may involve neoplastic T-cell death, psoralen adduct damage to cell organelles and alteration of the immune system.[20,21] These effects are elicited by nuclear damage to DNA resulting from the interaction of psoralen with DNA, as well as generation of singlet oxygen with subsequent cell membrane damage.[22] Recent studies on extracorporeal photopheresis attributed the induction of apoptosis to the dysregulation in the expression of the apoptotic genes Bcl-2 and Bax, and an increase of Fas/FasL system.[23]

The detailed mechanisms of action of narrowband UVB are not well defined. The therapeutic action in MF may involve a combination of effects, including changes in cell cycle kinetics, alterations in cytokine expression and immunomodulation. *In vitro* experiments show that UVB interferes with Langerhans cells and antigen presentation by reducing their viability and antigen function, and increases interleukin 2 and interleukin 6 production by human keratinocytes.[21,24] Increased levels of tumour necrosis factor have also been detected after UVB irradiation. Induction of T-cell apoptosis may also contribute to the suppression of the function of the neoplastic population of clonal T cells in the skin.[25] These effects are achieved with a low-rate adverse effects profile.

The acute adverse events of narrowband UVB include erythema, blistering, xerosis, pruritus and reactivation of herpes simplex.[15] However, these are easily managed and do not usually preclude treatment maintenance. Moreover, although UVB is a known carcinogen, its carcinogenic potential seems to be lower than that of PUVA;[26] nevertheless a small but significant increase of basal cell carcinomas was detected in a Scottish population survey.[27] In fact, narrowband UVB produced minimal side-effects in our patients. The adverse events rate, however, was not significantly different from that of PUVA therapy, an observation that is probably influenced by the sample size. The follow-up period was too short to report chronic adverse effects such as photoaging and photocarcinogenesis.

As for PUVA, the known side-effects associated with psoralen (nausea, vomiting and headache), the risk of excess phototoxicity, the interaction between UVA and the ocular lens, and the documented photocarcinogenesis and photoimmunosupression are unbalancing the choices in phototherapy towards narrowband UVB.[28] This is probably the main reason why a difference in age was found between our two study groups (Table 1): elderly patients frequently have more associated medical conditions that might contraindicate the use of PUVA.

This study confirms that phototherapy is a safe, effective and well-tolerated therapy in patients with early-stage CTCL, significantly delaying the time to recurrences. It should be expected of UVA to reach a better response initially and a longer disease-free remission because of the deeper radiation penetration. However, our results indicate that narrowband UVB is at least as effective as PUVA in treatment of early-stage MF. Larger series of patients are still needed, but as the use and indications of narrowband UVB phototherapy continue to increase, this study strengthens its role as a first-line therapy in MF.

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